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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,734	10/01/2003	Kevin H. Gardner	UTSD:1510-1	4912
23379	7590	09/04/2007	EXAMINER	
RICHARD ARON OSMAN			SWOPE, SHERIDAN	
4070 CALLE ISABELLA			ART UNIT	PAPER NUMBER
SAN CLEMEMTE, CA 92672			1652	
MAIL DATE		DELIVERY MODE		
09/04/2007		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10677734	10/1/2003	GARDNER ET AL.	UTSD:1510-1

EXAMINER

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ART UNIT      PAPER

1652      20070525

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Commissioner for Patents

This communication serves to correct errors in section (8) Evidence Relied Upon, in the Examiner's Answer mailed July 16, 2007.



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GROUP 1600

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/677,734

Filing Date: October 01, 2003

Appellant(s): GARDNER ET AL.

Richard Osman  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed March 19, 2007 appealing from the Office action mailed January 5, 2007.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

Appellants state that an appeal is pending in related application US 10/677,733 and that they are unaware of any other related appeals or interferences. The Examiner acknowledges that an appeal is pending in related application US 10/677,733. The Examiner is unaware of any other related appeals or interferences.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Amezcu et al, Structure and interactions of PAS kinase N-terminal PAS domain: model for intramolecular kinase regulation. *Structure*. 2002 Oct;10(10):1349-61.

Cusanovich et al, Photoactive yellow protein: a prototypic PAS domain sensory protein and development of a common signaling mechanism. *Biochemistry*. 2003 May 6;42(17):4759-70. Review.

Art Unit: 1652

Ema et al, A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1alpha regulates the VEGF expression and is potentially involved in lung and vascular development. Proc Natl Acad Sci U S A. 1997 Apr 29;94(9):4273-8.

Erbel et al, Structural basis for PAS domain heterodimerization in the basic helix-loop-helix-PAS transcription factor hypoxia-inducible factor. Proc Natl Acad Sci U S A. 2003 Dec 23;100(26):15504-9. Epub 2003 Dec 10.

Fukunaga et al, Identification of functional domains of the aryl hydrocarbon receptor. J Biol Chem. 1995 Dec 8;270(49):29270-8.

Naray-Szabo, Analysis of molecular recognition: steric electrostatic and hydrophobic complementarity. J Mol Recognit. 1993 Dec;6(4):205-10.

Taylor et al, PAS domains: internal sensors of oxygen, redox potential, and light. Microbiol Mol Biol Rev. 1999 Jun;63(2):479-506. Review.

Vogtherr et al, NMR-based screening methods for lead discovery. EXS. 2003;(93):183-202. Review.

#### **(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

I. Claim 21 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the full scope of the recited invention. The specification is enabling for a method of introducing the ligand KG-721 into the hydrophobic core of the human HIF2a PAS-B domain and, thereby, changing the surface binding properties of the PAS domain. However, the specification does not enable the skilled artisan to affect the surface binding of any HIF2a PASB domain by "introducing into the hydrophobic core of the PAS domain a [any] foreign ligand".

Claim 21 is so broad as to encompass a method changing the surface binding specificity of any HIF2a PAS-B domain using any steps that can introduce any ligand into the hydrophobic core of the PAS-B domain. The scope of this claim is not commensurate with the enablement

Art Unit: 1652

provided by the disclosure with regard to the large number of possible ligands and possible steps to be used for introducing the ligand into the hydrophobic core of any PAS-B domain and, thereby, changing the surface binding specificity.

The specific steps and ligands used for introducing a ligand into the hydrophobic core of the PAS domain determine the method's success. Predictability of which of the large number of possible steps and ligands to be used requires guidance with regard to how said steps and the structure of said ligands affect the desired binding in the hydrophobic core and alteration of surface binding specificity. However, neither the specification nor the prior art teach the skilled artisan how to direct, restrict, or control binding of any ligand to the hydrophobic core of any PAS domain. Therefore, the specification fails to teach "introducing into the hydrophobic core of the PAS domain a foreign ligand".

The specification does not support the broad scope of Claim 21, which encompasses any steps for introducing any ligand into the hydrophobic core of any HIF2a PAS-B domain and thereby change the surface binding specificity. The specification does not support the broad scope of Claim 21 because the specification does not establish: (A) which steps can be used to direct, restrict, or control introduction of any ligand into the hydrophobic core of any HIF2a PAS-B domain; (B) how any said steps may be altered, or not altered, and still obtain the desired effects; (C) the general tolerance of any successful method to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any steps of any method with an expectation of obtaining the desired binding in the hydrophobic core and, thus, change the surface binding specificity; (E) regions of any ligand's structure which may or may not be modified without effecting the desired binding in the hydrophobic core and change in the surface

Art Unit: 1652

binding specificity; (F) the general tolerance of the desired biological effect to modification of any ligand and extent of such tolerance; (G) a rational and predictable scheme for modifying any ligand with an expectation of obtaining the desired biological function; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices of steps and ligands is likely to be successful.

Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including using any steps for introducing any ligand into the hydrophobic core of any HIF2a PAS-B domain and, thus, change the surface binding specificity. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of steps and ligands having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

II. Claim 21 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention. This claim is directed to a genus of methods, wherein introducing a foreign ligand into the hydrophobic core of any HIF2a PAS-B domain results in a change in the surface binding specificity of the PAS domain. The specification teaches only a single representative species of such methods, wherein introduction of the ligand KG-721 into

Art Unit: 1652

the human HIF2a PAS-B domain hydrophobic core alters surface binding specificity (pg 18; Table 3, upper). Moreover, the specification fails to describe any other representative species of methods by any identifying characteristics or properties other than the functionality of introducing any a foreign ligand into the hydrophobic core of any HIF2a PAS-B domain and, thus, affecting the surface binding properties. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that Appellants were in possession of the claimed invention.

III. Claim 21 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995. Vogtherr et al teach an NMR-based method of detecting ligand binding to proteins, wherein binding is detected by  $^1\text{H}/^{15}\text{N}$ -HSQC NMR (Fig 2), while Amezcua et al specifically teach the use of  $^1\text{H}/^{15}\text{N}$ -HSQC NMR to detect ligand binding to the PAS domain of PAS kinase (Fig 4). Neither Vogtherr et al nor Amezcua et al teach the use of  $^1\text{H}/^{15}\text{N}$ -HSQC NMR to detect binding of a ligand to a HIF2a PAS-B domain. Ema et al teach the identification and characterization of HIF2a (HLF therein), which is a hypoxia-sensitive mediator of transcription comprising PAS domains A and B (Fig 1 & 3D). It would have been obvious to a person of ordinary skill in the art to use the method of Vogtherr et al or Amezcua et al to detect binding of compounds to the HIF2a PAS-B domain hydrophobic core. Suggestion to do so derives from the following, which would have been known to the skilled artisan. In response to hypoxia, HIF2a regulates transcription via the Arnt DNA binding protein (Ema et al; Table 1 & Fig 3). The aryl hydrocarbon receptor (Ahr) is a PAS domain-containing protein analogous to

Art Unit: 1652

HIF2a that regulates transcription in response to organic carcinogens. Like HIF2a, Ahr regulates transcription via the Arnt DNA binding protein (Fukunaga et al, 1995; Table 1). Thus, for each signaling pair of molecules, the HIF2a or Ahr is the “sensor” molecule, while Arnt is the transcriptional activator. Binding of organic carcinogens to Ahr is via Ahr’s PAS-B domain (Fukunaga et al; pg 29272, parag 2 & Table 1). A person of ordinary skill in the art would believe that, more likely than not, modulators of HIF2a also bind to the HIF2a PAS-B domain. Moreover, Amezcu et al teach that the hydrophobic core of PAS domains, including those that are well-packed and without an obvious cavity, are likely to have binding and sensor function (pg 1358, pargs 3-4). In order to identify modulators of the cell’s response to hypoxia, one would be motivated to use the method of Vogtherr et al or Amezcu et al to detect binding of compounds to the HIF2a PAS-B domain hydrophobic core. Motivation to do so derives from the desire to identify activators, inhibitors, and modulators of the cell’s response to hypoxia, which would have use in the treatment of cardiovascular diseases. The expectation of success is high, as methods using <sup>1</sup>H/<sup>15</sup>N-HSQC NMR to detect binding of ligands to proteins, including PAS domains, were known in the art. Therefore, Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcu et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995.

#### **(10) Response to Arguments**

##### **I. Is the full scope of the subject matter of Claim 21 enabled by the specification?**

Appellants provide the following arguments in response to the rejection of Claim 21 under 35 U.S.C. 112, first paragraph/enablement.

Art Unit: 1652

(A) Suitable foreign ligands may be screened from libraries of synthetic or natural compounds. The process was exemplified with the HIF2a PAS-B domain, wherein a library of 772 compounds was screened using  $^1\text{H}/^{15}\text{N}$ -HSQC NMR (pgs 13 & 18).

(B) From the 21 compounds identified as binding to the HIF2a PAS-B domain, the inventors developed a “lead” HIF2a PAS-B domain ligand (pg 31).

(C) The specification confirms that the foreign ligands bind the hydrophobic core of the HIF2a PAS-B domain (pg 18).

(D) The practitioner does not require any a priori structural characteristics of the recited “foreign ligand” to practice the method. The method also does not require any special steps or processes. Introduction of the foreign ligand into the hydrophobic core of the PAS domain can be effected by simply mixing a PAS domain-containing protein with the ligand in solution (pg 20).

(E) The Declaration filed under 37CFR 1.132 provides evidence that the skilled artisan would be able to practice the claimed invention. Relevant to the instant rejection, said declaration asserts that the HIF2a PAS-B domain is an art-recognized, defined protein (Erbel et al., 2003).

#### I. Examiner's Response

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is acknowledged that the specification teaches a method for screening libraries of compounds for binding to the human HIF2a PAS-B domain taught by Ema et al., 1997. However, the elected invention is not directed to a method of screening compounds for binding to a HIF2a PAS-B domain. The elected invention is directed to a “method of changing a

functional surface binding specificity of a selected PAS domain...comprising... introducing into the hydrophobic core of the PAS domain a foreign ligand...”. In order to practice the elected invention, the specification must provide guidance as to which foreign ligands are likely to bind to the hydrophobic core of any HIF2a PAS domain and, thereby, change a functional surface binding specificity of the PAS domain, or what are the structural characteristics necessary for said desired function. Alternatively, the specification must provide guidance as to the steps and conditions under which foreign ligands, which are not likely to spontaneously bind to the hydrophobic core, can be induced to do so. The needed guidance is not provided by the specification or the prior art.

The instant argument appears to reflect Appellants' belief that the scope of the recited invention encompasses first screening for a ligand that bind in the hydrophobic core of the HIF2a PAS-B domain and then using said ligand in a method for “changing a functional surface binding specificity”, as recited in Claim 21. In so far as the recited invention has a scope encompassing first screening for agents that bind in the hydrophobic core of the HIF2a PAS-B domain, Claim 21 is enabled and rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, as described above. However, the Examiner contends that the scope of the claim herein is broader than this, as the claimed methods are not in fact limited to such a combined screening assay/use method but also encompasses use of compounds in the absence of any screening steps. Such a method is not enabled for the reasons stated above.

(B) Reply: It is acknowledged that the specification discloses that Appellants screened 772 compounds for binding to the HIF2a PAS-B domain. It is also acknowledged that the specification, based on said screening, discloses a single “lead” HIF2a PAS-B domain ligand.

Art Unit: 1652

Thus, only 0.13% of the compounds screened were found to bind in the hydrophobic core, providing little expectation of success in identifying compounds having the desired activity. Moreover, the specification fails to provide guidance as to regions of said lead ligand's structure that may, or may not, be modified without effecting the desired ability to be introduced into the hydrophobic core of any HIF2a PAS-B domain, the general tolerance of the desired binding to modification of said ligand's structure and extent of such tolerance, a rational and predictable scheme for modifying said ligand with an expectation of obtaining the desired biological function, and the specification provides insufficient guidance as to which of the essentially infinite possible choices of modified ligands is likely to be successful.

(C) Reply: It is acknowledged that the specification confirms that the ligand KG-721 binds the hydrophobic core of the human HIF2a PAS-B domain (pg 18; Table 3, upper). However, as previously stated, the specification contains no guidance for the artisan with regards to other compounds that can be bound to the core simply by contacting the compound with the PAS domain. As is well-known in the art, binding between a protein and ligand is analogous to insertion of a key into a lock i.e., the "lock-and-key" model, wherein binding is dependent upon steric, electrostatic, and hydrophobic complementarity (Naray-Szabo, 1993). The skilled artisan understands that not all ligands will bind to any protein and that binding specificity provides functional specificity. Thus, not all ligands are expected to bind to any PAS-B domain; only specific ligands, whose structures were unpredictable and the time of filing, will bind. While the specification discloses a single ligand that binds to a single PAS-B domain, small variations in the structure of the protein and/or ligand can enormously alter the lock and key "fit" (Naray-Szabo,

Art Unit: 1652

1993). Guidance as to how any ligand can, or cannot, be altered and retain the desired binding to any HIF2a PAS-B domain, or any variant thereof, has not been provided.

(D) Reply: Using the “lock-and-key” analogy described above, changes in the PAS domain corresponds to changes in the “lock”, which will, more likely than not, require a different “key” for binding. Thus, the KG-721 ligand, which binds the hydrophobic core of the human HIF2a PAS-B domain, is unlikely to bind the full scope of PAS-B domains encompassed by the recited invention. As explained above for (A) above, in order for the skilled artisan to practice the elected invention, the specification must provide guidance as to (i) which foreign ligands are likely to bind to the hydrophobic core of any HIF2a PAS-B domain simply by contacting the ligand with the PAS-B domain, (ii) the relationship between structural characteristics of any ligand and the desired function, or (iii) which steps and conditions can be successfully used to induce any foreign ligand to bind to the PAS domain hydrophobic core. Such guidance has not been provided by the instant specification.

(E) Reply: The Declaration filed under 37CFR 1.132 by Dr. Stephen Sprang is acknowledged. Relevant to the instant rejection, it is acknowledged that the human HIF2a PAS-B domain is a defined protein. However, Claim 21 is not limited to methods using the human HIF2a PAS-B domain. The recited method encompasses using all naturally occurring HIF2a PAS-B domains, as well as variants thereof.

II. Is the full scope of the subject matter of Claim 21 described by the specification?

Appellants provide the following arguments in response to the rejection of Claim 21 under 35 U.S.C. 112, first paragraph/written description.

Art Unit: 1652

(F) Suitable foreign ligands may be screened from libraries of synthetic or natural compounds. The process was exemplified with the HIF2a PAS-B domain, wherein a library of 772 compounds was screened using  $^1\text{H}/^{15}\text{N}$ -HSQC NMR (pgs 13 & 18).

(G) From the 21 compounds identified as binding to the HIF2a PAS-B domain, the inventors developed a “lead” HIF2a PAS-B domain ligand (pg 31).

(H) The specification confirms that the foreign ligands bind the hydrophobic core of the HIF2a PAS-B domain (pg 18).

(I) The practitioner does not require any a priori structural characteristics of the recited “foreign ligand” to practice the method. The method also does not require any special steps or processes. Introduction of the foreign ligand into the hydrophobic core of the PAS domain can be effected by simply mixing a PAS domain-containing protein with the ligand in solution (pg 20).

(J) The Declaration filed under 37CFR 1.132 provides evidence that the skilled artisan would be able to practice the claimed invention. Relevant to the instant rejection, said declaration asserts that the HIF2a PAS-B domain is an art-recognized, defined protein (Erbel et al., 2003).

## II. Examiner's Response

These arguments are not found to be persuasive for the following reasons.

(F) Reply: This is the identical argument presented above for the rejection of Claim 21 under 35 U.S.C. 112, first paragraph/enablement. Again, it is acknowledged that the specification teaches a method for screening libraries of compounds for binding to the HIF2a PAS-B domain. However, the elected invention is not directed to a method of screening. The

Art Unit: 1652

elected invention is directed to a genus of methods for “changing a functional surface binding specificity of a selected PAS domain...comprising... introducing into the hydrophobic core of the PAS domain a foreign ligand...”. The specification describes a single species of the recited invention, wherein the surface binding specificity of the human HIF2a PAS-B domain is altered by introducing the compound KG-721 into the domain’s hydrophobic core (pg 18; Table 3, upper). However, this sole example of how to practice the elected invention, without additional descriptive means such as words, structures, figures, diagrams, or formulas that fully set forth the claimed invention, and in particular set forth the compounds which bind to any HIF2a PAS-B domain core simply by contacting the compound thereto, fails to sufficiently describe the invention such that a skilled artisan would recognize that Appellants were in possession at the time of filing.

Again, in as far as Appellants’ believe that the scope of the elected invention encompasses first screening for agents that bind in the hydrophobic core of the HIF2a PAS-B domain and then using identified ligands in a method for “changing a functional surface binding specificity”, Claim 21 is described and rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcu et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, as explained above.

(G) Reply: As explained in (F) above, Appellants’ sole example of how to practice the elected invention, without additional descriptive means such as words, structures, figures, diagrams, or formulas that fully set forth the claimed invention, fails to sufficiently describe the invention such that the skilled artisan would recognize that Appellants were in possession at the time of filing. Said one example is not representative of all possible methods encompassed by the

Art Unit: 1652

claim because it does not describe the scope of ligands to be used or the scope of steps and reagents to be used to obtaining the desired biological effect. In particular, the specification does not describe any ligand, other than KG-721, that can be successfully used in the recited invention or regions of any ligand's structure that may or may not be modified to obtain the desired binding in the hydrophobic core and change in the surface binding specificity. The specification also does not describe which steps can be used to direct, restrict, or control introduction of any ligand into the hydrophobic core of any HIF2a PAS-B domain or how any said steps may, or may not, be altered and still obtain the desired effects. Thus, the claim contains subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention.

(H) Reply: It is acknowledged that the specification confirms that the ligand KG-721 binds the hydrophobic core of the human HIF2a PAS-B domain (pg 18; Table 3, upper).

(I) Reply: In order for the skilled artisan to recognize that Appellants were in possession of the elected invention, the specification should disclose either (i) which foreign ligands are likely to bind to the hydrophobic core of the PAS domain, (ii) the relationship between structural characteristics and the desired function, or (iii) which steps and conditions can be successfully used to induce any foreign ligand to bind to the PAS domain hydrophobic core. Such disclosure is not provided and, thus, the invention is not described in a manner whereby the skilled artisan would recognize that Appellants were in possession at the time of filing.

Again, in as far as Appellants' believe that the scope of the recited invention encompasses first screening for agents that bind in the hydrophobic core of the HIF2a PAS-B

Art Unit: 1652

domain by simple mixing and then using identified ligands in a method for “changing a functional surface binding specificity”, Claim 21 is described and rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, as explained above. However, again, the Examiner contends that the scope of the claim herein is broader than this, as the claimed methods are not in fact limited to such a combined screening assay/use method but also encompasses use of compounds in the absence of any screening steps. Said method is not described for the reasons stated above.

(J) Reply: The Declaration filed under 37CFR 1.132 by Dr. Stephen Sprang is acknowledged. Relevant to the instant rejection, it is acknowledged that the human HIF2a PAS-B domain is a defined protein. However, Claim 21 is not limited to methods using the human HIF2a PAS-B domain. The recited method encompasses using all naturally occurring HIF2a PAS-B domains, as well as variants thereof. It is also noted that Erbel et al, 2003 was published after the filing date of the instant application.

III. Is the subject matter of Claim 21 properly rejected under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995?

Appellants provide the following arguments in response to the rejection of Claim 21 under 35 U.S.C. 103(a).

(K) Prior to the present disclosure, HIF was known to be regulated by oxygen via mechanisms not involving the PAS domains.

Art Unit: 1652

(L) The Action correctly states that the inventors' prior publication (Amezucua et al, 2002) discloses that the PASK PAS-A domain has a well-packed core, yet was able to bind small molecules. It is also acknowledged that said publication speculates that other well-packed PAS domain may serve as sensors. However, the PASK PAS-A domain also exhibited "unusual flexibility ...near the ligand binding sites" (Amezucua et al, pg 1352, col 1, lines 10-12). In contrast, the well-folded HIF2a PAS-B domain lacks the dynamic regions of PASK PAS-A (Amezucua et al, 2002). In addition, unlike PASK, HIF2a was known to be regulated by mechanisms not involving the PAS domains. Such structural and functional distinctions between HIF2a and PASK removes an expectation of ligand binding to the HIF2a PAS-B domain core based on the structure and function of PASK.

(M) The HIF2a PAS-B domain is well-folded and lacking the long insertion loops of NPAS2 PAS-A (Erbel et al, 2003), also removing an expectation of ligand binding to the core.

(N) An expert's Declaration provides [uncontroverted] evidence that one of skill in the art would not have expected a HIF2a PAS domain to provide a core for sensory binding.

### III. Examiner's Response

These arguments are not found to be persuasive for the following reasons.

(K) Reply: It is acknowledged that the art teaches that non-PAS domain mediated mechanisms can regulate the response of HIF to oxygen. However, said teachings do not provide a *prima facie* case against the PAS domain modulating an effect of oxygen or mediating the effect of other ligands on HIF. PAS domains were known to be sensory via binding of ligands to their hydrophobic core (Taylor et al, 1999; Cusanovich et al, 2003; esp pg 4765-4769). Also, see (L) below.

Art Unit: 1652

(L) Reply: It is acknowledged that Amezcua et al state that a reason they predicted that the PASK PAS-A domain binds organic compounds is that said domain is flexible in the region analogous to the ligand binding sites for other PAS domains. The fact that the PASK PAS-A domain is flexible in said region does not provide a *prima facie* case against the HIF2a PAS-B domain binding ligands within its core.

Amezcua et al clearly state, as the first reason they predicted that the PASK PAS-A domain binds organic compounds, that organic compounds play a key role in PAS domain signaling processes (pg 1352, parg 1). Moreover, it was accepted at the time of filing that PAS domains are signaling modules that monitor changes in environmental conditions via core-bound molecules (Taylor et al, 1999; pg 480, parg 1; pg 488, parg 3; pg 490, parg 3). Furthermore, Cusanovich et al clearly teach that PAS domains have a common signaling mechanism, whereby a ligand bound in the central core alters associated hydrophobic residues leading to an alteration in the surface binding characteristics of the domain (pg 4767). In fact, Appellants' own publication states that "well-pack hydrophobic cores that lack any obvious cavities for binding ...does not preclude the use of such domains as sensors" (Amezcua et al; pg 1358, parag 4), indicating that Appellants were aware, at the time of filing, that well-packed PAS domains will serve as sensors. Thus, each of Amezcua et al, Taylor et al, and Cusanovich et al teach an expectation that essentially any PAS domain will bind a ligand in its core and serve as a sensor. Lacking evidence to the contrary, the skilled artisan would have believed that, more likely than not, any PAS domain would bind a ligand within it's hydrophobic core .

(M) Reply: Any teachings of Erbel et al are not relevant to the instant rejection, since Erbel et al was published after the filing date of the application. Nonetheless, the fact that the

Art Unit: 1652

HIF2a PAS-B domain lacks the long insertion loops of NPAS2 PAS-A does not provide a *prima facie* case against the HIF2a PAS-B domain binding ligands within its core.

(N) Reply: The Declaration filed under 37CFR 1.132 by Dr. Stephen Sprang is acknowledged. Relevant to the instant rejection, Dr. Sprang makes the following statements. (i) Prior to the present disclosure, HIFa was known to be regulated by oxygen via mechanisms not involving the PAS domains. (ii) The HIF2a PAS-B domain presents a well-folded domain, which significantly contrasts with the dynamic regions of PASK PAS-A, removing an expectation of core ligand binding. (iii) The apo-structure of the HIF2a PAS-B domain is in contrast with the apo-structure of many small ligand-binding protein domains, which either exhibit pre-formed cavities or adopt an unfolded conformation.

These statements are not found to be persuasive for the following reasons.

(i) See (K) above.

(ii) Appellants' own publication teaches that PAS domains containing well-packed hydrophobic cores, lacking any obvious cavity for binding of small ligands, and folding stably in a ligand-free state are not precluded from functioning as sensors by binding ligand in the core (Amezcua et al; pg 1358, parg 4-5). Amezcua et al further state that, "a very broad range of PAS domains, including those that do not copurify with ligands when isolated from natural sources, may serve sensor roles in vivo" (pg 1358, parg 5). Therefore, Amezcua et al clearly suggest that PAS domains having a tightly packed core, such as the HIF2a PAS-B domain, may still bind small molecules within their core and act as sensors. Moreover, it was accepted at the time of filing that PAS domains are signaling modules that monitor changes in environmental conditions via core-bound molecules (Taylor et al, 1999; pg 480, parg 1; pg 488, parg 3; pg 490, parg 3).

Art Unit: 1652

Furthermore, Cusanovich et al clearly teach that PAS domains have a common signaling mechanism, whereby a ligand bound in the central core alters associated hydrophobic residues leading to an alteration in the surface binding characteristics of the domain (pg 4767). Thus, each of Amezcua et al, Taylor et al, and Cusanovich et al teach that essentially any PAS domain will bind a ligand in its core. Lacking evidence to the contrary, the skilled artisan would have believed that, more likely than not, any PAS domain would bind a ligand within it's hydrophobic core.

(ii) It is acknowledged that PAS domains are different from other ligand-binding domains. However, based on the state of the art at the time of filing, the skilled artisan would have believed that, more likely than not, the HIF2a PAS-B domain would bind a ligand within its hydrophobic core and serve as a sensor; see (L) above.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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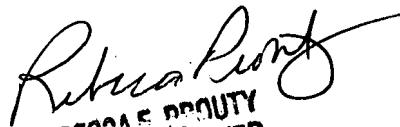
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